HYALURONIC ACID GEL SLURRY AND ITS USE

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Abstract of JP 2000230001 (A)

PROBLEM TO BE SOLVED: To provide a medical material with an especially high biocompatibity by incorporating a gel formed from hyaluronic acid alone into the same. SOLUTION: The gel is a self-crosslinked one formed from hyaluronic acid alone without using any other crosslinker or modifier and without forming a composite with a cationic polymer, Preferably, the gel is crushed with a suitable crusher to an average particle size of 10 mm or smaller. The resultant particulate hyaluronic acid gel is neutralized with a phosphoric-acid-buffered physiological salt solution which has a pH of 7 and is prepared by adding a phosphoric acid buffer component in a concentration of 50 mM to a physiological salt solution.; The neuralized particulate gel is washed with water for injection and then suspended in a concentration of 0.1-5 wt.% in an arbitrary solution, giving a gel slurry, The slurry is suitable for in-vivo decomposable medical materials, cosmetics, etc.

FULL CONTENTS

[Claim(s)]
[Claim 1]Hyaluronic acid gel slurry containing a gel formed by a hyaluronic acid independent.
[Claim 2]The hyaluronic acid gel slurry according to claim 1 whose mean particle diameter of a gel formed by a hyaluronic acid independent is 10 mm or less.
[Claim 3]The hyaluronic acid gel slurry according to claim 1 or 2 whose slurry concentration of a gel formed by a hyaluronic acid independent is 0.1 to 5 weight %.
[Claim 4]A biomedical material containing hyaluronic acid gel slurry of a description in any 1 paragraph of Claims 1-3.
[Claim 5]A cosmetic containing hyaluronic acid gel slurry of a description in any 1 paragraph of Claims 1-3.

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates especially to those biomedical materials about hyaluronic acid gel slurry containing the gel formed by a hyaluronic acid independent.
[0002]
[Description of the Prior Art]Hyaluronic acid is polymer polysaccharide of the straight chain shape which beta-D-N-acetylglucosamine and beta-D-glucuronic acid combined by turns. Hyaluronic acid is distributed over the connective tissue of a mammal, and also existence is known by that of a chicken, the kapsel of ** and a streptococcus, etc. That of a chicken, **, funiculus umbilicalis, etc. is used as an extraction material, and also refining things are adjusted from the culture of the streptococcus. Hyaluronic acid does not have a kind and organ specificity, but it is known that the biocompatibility which was excellent even if it was a case where it transplanted or poured into a living body is shown.
[0003]The demerit originating in the easy water-solubility of the hyaluronic acid in the case of applying to a living body itself, for example, the chemical modification thing of various hyaluronic acid is also proposed from residence time in the living body being comparatively short etc. (a U.S. Pat. No. 4,582,865 Description.) Refer to JP,H6-37575,B, JP,H7-97401,A, JP,S60-130601,A, JP,H3-105003,A, European patent 0341745A1, and JP,H6-73103,A.
[0004]Hyaluronic acid has very high ********** and moistness, it does not essentially have antigenicity, and since biocompatibility is high, it is used for a remedy, an ophthalmic surgery adjuvant, etc. of gonarthrosis. Although using as an antiadhesive

material after performing an operation on the hyaluronan solution itself is also examined, Since reservoir nature in the living body is comparatively short, and an effect is weak and water solubility, it spreads and flows from a wound surface for a short time (Journal of Gynecologic Surgery vol.7 No.2 97-101 (1991).).
[0005]The outstanding feature of biocompatibility which hyaluronic acid itself originally has, [a maximum student or ** sake] Residence time in the living body usable as a biocompatibility biomedical material found out the long hyaluronic acid gel, without [without it uses a chemical cross linking agent and a chemical modification agent in any way, and] complex-izing with a cationic polymer (PCT/JP 98/No. 03536).
[0006]The biomedical material formed by the hyaluronic acid independent used as an antiadhesive material and wound therapy material is fabricated by the sheet shaped, and reveals an effect by sticking on a surgical operation part directly. However, in the case of the surgical operation of the part where the sheet used the endoscope etc., operativity is not good. Application to the part where a minute part and shape are complicated is also difficult.
[0007]
[Problem to be solved by the invention]In big mean particle diameter, uniform administration is difficult for the grains produced by this invention persons doing crushing treatment of the gelled hyaluronic acid, or the hyaluronic acid gel particle produced by freezing a low concentration hyaluronic acid nature aqueous solution to the part where a minute part and shape are complicated. Then, uniform application to the part where a minute part and shape are complicated was made possible by mean particle diameter being 10 mm or less. By preparing slurry concentration to 0.1 to 5weight %, suitable flowability is held, and it finds out that it is effective also as an injecting material and this hyaluronic acid gel slurry is still more useful also as a biomedical material and a cosmetic, and came to complete this invention.
[0008]
[Means for solving problem]Namely, hyaluronic acid gel slurry, wherein this invention contains the gel formed by (1) hyaluronic-acid independent, (2) Hyaluronic acid gel slurry given in (1) the given mean particle diameter of the gel formed by a hyaluronic acid independent is 10 mm or less, (3) (1) or hyaluronic acid gel slurry given in (2) whose slurry concentration of the gel formed by a hyaluronic acid independent is 0.1 to 5 weight %, (4) It is a cosmetic containing hyaluronic acid gel slurry given in any 1 paragraph of (1) biomedical material [containing hyaluronic acid gel slurry of a description in any 1 paragraph of - (3)], (5), and (1) - (3).
[0009]
[Mode for carrying out the invention]Hereafter, this invention is explained in detail. The thing extracted from animal tissue can also be used for the hyaluronic acid used for this invention, without asking the origin also by what was manufactured with bacterial coupling. The microorganism which has hyaluronic acid productivity, such as a streptococcus group into which the strain used with bacterial coupling is separated from a nature, Or Streptococcus-equi FM-100 (Fermentation Research Institute mycoparasite No. 9027) indicated to JP,S63-123392,A, The variant which produces hyaluronic acid stably with high yield like Streptococcus-equi FM-300 (Fermentation Research Institute mycoparasite No. 2319) indicated to JP,H2-234689,A is desirable. What used the above-mentioned variant, and was cultivated and refined is used.

[0010]With the gel formed by the hyaluronic acid independent as used in the field of this invention, the three-dimensional network is formed of the structure of cross linkage of hyaluronic acid. When it carries out that it is poorly soluble to a neutral water solution with the feature and this hyaluronic acid gel is supplied in a neutral water solution, significant poor solubility is shown as compared with the hyaluronic acid which is not gelled. Maintenance of the form of the gel in the inside of a 37 ** neutral aqueous solution and the dissolution rate of a gel prescribe poor solubility. When the hyaluronic acid gel as used in the field of this invention is supplied in an alkaline aqueous solution, for example, the alkaline buffer solution of pH 11, it also has the feature dissolved promptly.
[0011]The gel formed by the hyaluronic acid independent as used in the field of this invention is making a gel form by not complex-izing with that neither a chemical cross linking agent nor a chemical modification agent uses it and a cationic polymer in addition to hyaluronic acid, and means the gel which carried out self-bridge formation.
[0012]The thing of about $1x10^5$ - abbreviation $1x10^7$ Dalton within the limits of the molecular weight of the hyaluronic acid used for this invention is preferred. If it has the molecular weight in a mentioned range, what was obtained more from the thing of the amount of polymers by carrying out hydrolysis treatment etc. can be used preferably similarly. The hyaluronic acid said to this invention is used with the concept which also includes the salt of the alkali metal salt, for example, sodium, potassium, and lithium.
[0013]The hyaluronic acid gel as used in the field of this invention can be decomposed and solubilized by processing a hyaluronic acid gel under the promotion acidic hydrolysis reaction conditions of hyaluronic acid. When the solubilized hyaluronic acid holds the structure of cross linkage, it can distinguish from hyaluronic acid of straight chain shape in polymer solution theory as hyaluronic acid which has a turning point.
[0014]As promotion acidic hydrolysis reaction conditions of hyaluronic acid as used in the field of this invention, pH 1.5 temperature of 60 ** of an aqueous solution is suitable. The principal chain cutting reaction by hydrolysis of the glycosidic linkage of hyaluronic acid is remarkably promoted [be / it / under / neutral aqueous solution / comparison] in acidity or an alkaline aqueous solution. As for an acidic hydrolysis reaction, the one where reaction temperature is higher is promoted.
[0015]In this invention, the molecular weight and degree of branching of the molecular weight fraction which were separated by GPC were continuously measured on-line using the GPC-MALLS method. In this invention, the degree of branching was measured using the elution volume method which calculates a degree of branching by measuring the molecular weight of straight-chain-shape hyaluronic acid used as the molecular weight of the hyaluronic acid by which the fraction of the same elution volume was solubilized, and control. A degree of branching is the number of the turning points which exist in per polymer chain of the solubilized hyaluronic acid, and is plotted to the molecular weight of the solubilized hyaluronic acid.
[0016]The solubilized hyaluronic acid was diluted with the GPC solvent, prepared concentration, and after filtering with a 0.2-micrometer membrane filter, it presented measurement with it. When there is the structure of cross linkage which exists stably also under the promotion acidic hydrolysis conditions of hyaluronic acid in the hyaluronic acid gel as used in the field of this invention, branching structure is checked by the solubilized hyaluronic acid in polymer solution theory. The degree of branching of the

hyaluronic acid gel as used in the field of this invention is 0.5 or more.
[0017]The aqueous solution of hyaluronic acid mixes the powder and water of hyaluronic acid, and it is obtained by agitating. It is obtained also by the method of supplying hyaluronic acid to the water prepared into acidity from the acid. As for the concentration of this hyaluronic acid, 5.0 or less weight % is convenient on treatment of an aqueous solution. Any acid can be used for it if the acid used in order to adjust the pH of the aqueous solution of hyaluronic acid is an acid which can be adjusted to pH 2.0 or less. In order to reduce the amount of the acid used, it is desirable to use strong acid, for example, nitric acid, hydrochloric acid, sulfuric acid, etc. preferably.
[0018]After pouring freezing of a hyaluronan acid nature aqueous solution into arbitrary containers, it is performed at -30 **--10 ** temperature. Freezing is good by the method of freezing from the bottom, and any method of freezing by an air system. After freezing for 4 hours or more, the hyaluronic acid gel was obtained by thawing, but when it was short-time freezing and the hyaluronic acid gel with a low gelling rate was prolonged freezing, the hyaluronic acid gel with a high gelling rate was obtained, and suitable slurry has been manufactured by crushing and carrying out suspension treatment also of any.
[0019]The following grinder is chosen by the degree of crushed grain which makes crushing of a hyaluronic acid gel the purpose. The crushing type (a brake, Dodge, a single, a TOGGURU jaw crusher) of a compression grinding method, a whirling type (JAIRETORI, a cone, a Hydrocone crusher), a rotated type (a roll crusher, a single roll crusher, a disk crusher). the hand mill type (stamp mill) of an implosion grinding method, and a hammer die (a hammer mill.) An impact crusher, an impeller breaker, a Raymond vertical mill, A titanium mill, Novo Rota, a micron mill, a disintegrator, DISUMEMBURETA, a fluid energy type (a jet mill, Jett Pal Pella Ihza, micro NAIZA, and RIDAKUSHONAIZA jet crusher, EYAMIRU), a rotating cylinder type (contest a bird [a ball an inner tube, a compartment, a rod conical one, and], a HIRUDE brand mill). The rotated type of a shear grinding method (a cutting mill, a shear roll mill, you HIMIRU). The rotated type of a friction grinding method (a hand mill, a pan mill, an attrition mill, an age runner), A whirling type (a screw crusher, a column type mill, a side glider), Although a centrifugal force type (a centrifugal roller mill, a centrifugal ball mill), a rotating cylinder type (a ring roller mill, high-speed ball mill, and low-speed ball mill, a Hyswing ball mill, a vibration ball mill), a wet colloid mill type (pre MIYAMIRU, SHAROTTEMIRU), an ultrasonic crushing method, etc. are used, If crushing is possible, it will not be limited to these.
[0020]The crushing mean particle diameter of a hyaluronic acid gel is 10 mm or less, and is 10-5000 micrometers preferably.
[0021]After the phosphoric acid buffer physiological sodium chloride solution of pH 7 which added the phosphoric acid buffer component to physiological sodium chloride solution by 50mM concentration, and prepared the granular hyaluronic acid gel obtained by crushing a hyaluronic acid gel neutralizes, water for injection washes. Hyaluronic acid gel slurry is obtained by suspending the obtained granular hyaluronic acid gel in 0.1 to 5 weight % of slurry concentration in arbitrary solutions.
[0022]Next, the manufacturing method of slurry using the granular hyaluronic acid gel produced by freezing the low concentration hyaluronan acid nature aqueous solution used for this invention is explained. Preparation of the aqueous solution of hyaluronic acid is the same as that of the time of the method of granulating by crushing.

[0023]Hyaluronan concentration is 0.005 to 0.5 weight %, and its 0.01 to 0.2 weight % is preferred. It is because a gel is not fabricated at 0.005 or less weight %, and a hyaluronic acid gel granular at 0.5 weight % or more is not obtained but the hyaluronic acid gel of the lump depending on container shape is obtained.
[0024]Next, the pH of the aqueous solution of hyaluronic acid is prepared to 0.5-2.0. Any acid can be used if it is an acid which can be adjusted to pH 2.0 or less. In order to reduce the amount of the acid used, it is preferred to use strong acid, for example, nitric acid, hydrochloric acid, sulfuric acid, etc. preferably.
[0025]After pouring freezing of this low concentration hyaluronan acid nature aqueous solution into arbitrary containers, it is performed at -30 **--10 ** temperature. -Advance of gelling in freezing temperature lower than 30 ** is slow, and since a long time is needed, it is not desirable. A solution may not be frozen at a high temperature and it is not more desirable than -5 **.
[0026]Freezing is good by the method of freezing from the bottom, and any method of freezing of an air system. After freezing two days or more, a granular hyaluronic acid gel is obtained by thawing.
[0027]After a membrane filter recovers a granular hyaluronic acid gel for the aqueous acids concerned containing the granular hyaluronic acid gel obtained by freezing a low concentration hyaluronan acid nature solution, After the phosphoric acid buffer physiological sodium chloride solution of pH 7 which added the phosphoric acid buffer component to physiological sodium chloride solution by 50mM concentration, and was prepared neutralizes, water for injection washes. Hyaluronic acid gel slurry is obtained by suspending the obtained granular hyaluronic acid gel in 0.1 to 5 weight % of slurry concentration in arbitrary solutions. As for manufacture of slurry, after water for injection washes, it is possible to also make the freeze-dried thing again suspended in arbitrary solutions.
[0028]The hyaluronic acid gel slurry obtained by this invention can be especially used without restriction, if it is a field for which a general biodegradation nature biomedical material and hyaluronic acid are used. For example, the carrier of an antiadhesive material and a pharmacological activity substance, wound dressing, artificial skin, Organization substitution type body tissue restorative materials, joint infusion, skin infusion, the suture for surgical operations, Biomedical products or medicine constituents, such as a medical device, a medical supply, etc. used for a hemostat, an artificial organ, an artificial extracellular matrix or artificial basement membrane, diagnosis, and a therapy, And the use to cosmetics, such as a one spot cosmetic, various cream, a milky lotion, face toilet, an essence, a packing agent, a under makeup, foundation, jellies, and ointment, is mentioned.
[0029]Hyaluronic acid gel slurry can expect enhancement of an effect by the combination formula by mixing, mixing with the hyaluronic acid which is not used together and also gelled, or concomitant use with a different hyaluronic acid gel form, though use with a single form is natural. For example, when the combination of hyaluronic acid gel sheet-like moldings and a hyaluronan solution is used together for the slurry which consists of a hyaluronic acid gel as a postoperative antiadhesive material at an abdomen, a local effect and the whole intra-abdominal effect can be expected.
[0030]Next, an antiadhesive material is explained among the biomedical materials of this invention. As for the antiadhesive material of the granular hyaluronic acid gel slurry

obtained by this invention, it is preferred for it to be used for a surgical operation and to medicate a surgical operation part directly. The antiadhesive material of hyaluronic acid gel slurry can be applied to any animals which adhesion produces, and can prevent the adhesion after an operation suitably in a mammal, especially a human being.
[0031]Abdominal surgery, a gynecological surgery, a chest operation, an orthopedics operation concerning a tendon or a ligament, a neurosurgery operation concerning dura mater, etc. concerning the various organs in the abdominal cavity and the thorax, a tendon sheath, a cranium, a nerve, an eyeball, etc. of an administration place in the living body are useful anywhere.
[0032]Although any time when postoperative adhesion can be prevented may be sufficient as the time for administration of the antiadhesive material of the granular hyaluronic acid gel slurry obtained by this invention and it can be prescribed for the patient at the time during an operation of the end of an operation, it is preferred to prescribe a medicine for the patient especially just before the end of an operation.
[0033]
[Working example]Hereafter, a work example explains this invention in more detail. Thereby, this invention is not limited.
[0034]Work-example 1 molecular weight dissolved hyaluronate sodium of $2x10^6$ Dalton in water for injection, and adjusted 1weight % of the hyaluronic acid aqueous solution. The pH of this aqueous solution was adjusted the pH to 1.5 with 1N hydrochloric acid, and the hyaluronan acid nature aqueous solution was obtained. 80 ml of this hyaluronan acid nature aqueous solution was put into a 100-ml sample bottle, and was put into the freezer set as -20 **. The hyaluronic acid gel was obtained by freezing of 120 hours. Next, after repeating washing which adds 10 ml of water for injection, and carries out after-neglect decantation of this for 10 minutes 3 times, After repeating twice the neutralization which adds and carries out decantation of 100 ml of the phosphoric acid buffer physiological sodium chloride solution of pH 7 which added the phosphoric acid buffer component to physiological sodium chloride solution by 50mM concentration, and was adjusted, water for injection fully washed and the hyaluronic acid gel was obtained. A hyaluronic acid gel is added so that slurry concentration may be adjusted into arbitrary solutions according to the experiment of the following table 1, When crushing treatment was carried out using the micro homogenizer (NISSEI EXCEL AUTO HOMOGENIZER), slurry containing the granular hyaluronic acid gel whose mean particle diameter is 300-1,000 micrometers was obtained. Operation of these series was performed under sterile and non-dust environment, and the drug solution etc. to be used used what performed sterilization treatment beforehand.
[0035]Work-example dyad quantity dissolved hyaluronate sodium of $2x10^6$ Dalton in water for injection, and adjusted 0.01weight % of the hyaluronic acid aqueous solution. The pH of this aqueous solution was adjusted the pH to 1.5 with 1N hydrochloric acid, and the low concentration hyaluronan acid nature aqueous solution was obtained. 8 l. of this low concentration hyaluronan acid nature aqueous solution was put into a 10-l. container, and was put into the freezer set as -20 **. The granular hyaluronic acid gel with a mean particle diameter of 100-500 micrometers was obtained by freezing of 120 hours. After a membrane filter recovers a granular hyaluronic acid gel for the aqueous acids concerned containing a granular hyaluronic acid gel, After repeating washing which adds and carries out after-neglect decantation of 10 ml of the water for injection for 10

minutes 3 times, The neutralization which adds and carries out decantation of 100 ml of the phosphoric acid buffer physiological sodium chloride solution of pH 7 which added the phosphoric acid buffer component to physiological sodium chloride solution by 50mM concentration, and was adjusted was repeated twice, and water for injection fully washed. When it added and the hyaluronic acid gel was carried out so that slurry concentration might be adjusted into arbitrary solutions according to the following experiment, hyaluronic acid gel slurry was obtained. Operation of these series was performed under sterile and non-dust environment, and the drug solution etc. to be used used what performed sterilization treatment beforehand.

[0036]

[Table 1]

実験 No.	ヒアルロン酸ゲルスラリーの調整方法					
	ゲル調製		ゲル重量 [g]	溶液		スラリー濃度 [重量%]
	種類	平均粒径 [μm]		種類	液量[ml]	
1	実施例1	1,000	0.8	生理食塩水	80	1.0
2	実施例1	300	0.8	生理食塩水	80	1.0
3	実施例1	300	0.8	生理食塩水	27	3.0
4	実施例1	300	0.8	PBS	80	1.0
5	実施例1	300	0.8	PBS	27	3.0
6	実施例1	300	0.8	0.5% HA	80	1.0
7	実施例1	300	0.8	1.0% HA	80	1.0
8	実施例2	500	0.8	生理食塩水	80	1.0
9	実施例2	100	0.8	生理食塩水	80	1.0
10	実施例2	100	0.8	生理食塩水	27	3.0
11	実施例2	100	0.8	PBS	80	1.0
12	実施例2	100	0.8	PBS	27	3.0
13	実施例2	100	0.8	0.5% HA	80	1.0
14	実施例2	100	0.8	1.0% HA	80	1.0

[0037]The following examinations were presented with the granular hyaluronic acid gel obtained in degree-of-branching measurement work examples 1 and 2 of the work-example 3 hyaluronic-acid gel.

[0038]The hyaluronic acid gel was immersed in 15 ml of pH 1.5 hydrochloric acid aqueous solutions, it hydrolyzed at 60 ** for 6 hours, and the gel was made to solubilize completely. After having diluted this with the GPC solvent twice, adjusting concentration to 0.05weight % and filtering with a 0.2-micrometer membrane filter, as a result of pouring in 0.1 ml and measuring by GPC-MALLS, each degree of branching was 0.5 or more.

[0039]The following examinations were presented with the hyaluronic acid gel slurry obtained in each experiment of the soluble examination table 1 of work-example 4 hyaluronic-acid gel slurry.

[0040]The phosphoric acid buffer component was added to the physiological saline by

50mM concentration, and pH 7 phosphate buffered saline was prepared. The with 1.0 weight % and a mean particle diameter of 1,000 micrometers hyaluronic acid gel slurry suspended in the physiological saline obtained by experiment No.1, The with 1.0 weight % and a mean particle diameter of 300 micrometers hyaluronic acid gel slurry suspended in the physiological saline obtained by experiment No.2, The with 1.0 weight % and a mean particle diameter of 300 micrometers hyaluronic acid gel slurry suspended in PBS obtained by experiment No.4, 1.0 weight % suspended in the 0.5 weight % hyaluronan solution obtained by experiment No.6, 1.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers and the physiological saline obtained by experiment No.8, 1.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 500 micrometers and the physiological saline obtained by experiment No.9, Hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers, 1.0 weight % suspended in PBS obtained by experiment No.11, 1.0weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and the 0.5 weight % hyaluronan solution obtained by experiment No.13, hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and 1 ml of each were immersed in 50-ml phosphoric acid **********, and were agitated gently. It asked for the rate of the hyaluronic acid eluted in phosphate buffered saline at 37 ** from the hyaluronan concentration in phosphate buffered saline. The result is shown in Table 2.

[0041]It asked for the hyaluronan concentration in the measurement phosphate buffered saline of hyaluronan concentration from the peak area of the differential refractive index detector using GPC.

[0042]

[Table 2]

実験No	ヒアルロン酸ゲルスラリーの溶解率〔%〕					備考
	12時間後	1日後	2日後	7日後	14日後	
15	2	3	4	16	53	実験No. 1
16	1	3	5	15	55	実験No. 2
17	0	1	3	16	50	実験No. 4
18	0	2	5	17	58	実験No. 6
19	0	1	3	16	55	実験No. 8
20	1	2	4	14	59	実験No. 9
21	2	3	6	18	60	実験No. 11
22	2	4	6	17	59	実験No. 13

[0043]It was checked from Table 2 that hyaluronic acid gel slurry shows effective reservoir nature.

[0044]The following examinations were presented with the hyaluronic acid gel slurry obtained by experiment No.2-5 and experiment No.9 - 12 by considering the adhesion preventive effect examination hyaluronic acid aqueous solution by the mouse womb model of a work-example 5 hyaluronic-acid gel slurry antiadhesive material as comparison.

[0045]The 7 weeks-old female ICR mouse (weights 25-30g) was made an incision in the abdomen by postanesthetic midline incision by intra-abdominal pentobarbital injection, and damage was added to cornu uteri by iodine tincture scratch spreading by a length of about 10 mm. 1.0 weight % suspended in the physiological saline obtained by the mouse of each ten groups by no taking a measure and experiment No.2 as control, 3.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers and the physiological saline obtained by experiment No.3, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers, 1.0 weight % suspended in PBS obtained by experiment No.4, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers, 3.0 weight % suspended in PBS obtained by experiment No.5, 1.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers and the physiological saline obtained by experiment No.9, 3.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and the physiological saline obtained by experiment No.10, Hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers, 1.0 weight % suspended in PBS obtained by experiment No.11, The hyaluronic acid aqueous solution was used 1.0weight % as hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and comparison 3.0weight % suspended in PBS obtained by hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and experiment No.12.
[0046]A hyaluronic acid aqueous solution and 1 ml of hyaluronic acid gel slurry were added to the damaged area, and the closed belly was carried out in 5-0 DEKISON.
[0047]It carried out the resumption belly of the abdomen each for ten mice which prescribed no taking a measure, hyaluronic acid gel slurry, and a hyaluronic acid aqueous solution for the patient after cervical vertebrae dislocation fatality on the 10th day of after the operation, and the existence of adhesion formation was judged. The very slight adhesion with filmy adhesion formation was not judged to be adhesion, but it was fibrous, and was thick and the case where the strong adhesion which is not easily stripped as **** with pincettes was produced was judged to be adhesion. The result is shown in Table 3.
[0048]
[Table 3]

実験No.	実験群	癒着発生匹数	備考
23	無処置群	9／10	比較例
24	ヒアルロン酸水溶液	5／10	比較例
25	実験No. 2	0／10	実施例
26	実験No. 3	0／10	実施例
27	実験No. 4	1／10	実施例
28	実験No. 5	0／10	実施例
29	実験No. 9	1／10	実施例
30	実験No. 10	1／10	実施例
31	実験No. 11	1／10	実施例
32	実験No. 12	1／10	実施例

[0049]From Table 3, when the formation rate of adhesion with no taking a measure is nine animals among ten animals, a hyaluronic acid aqueous solution among ten animals 1.0weight % Six animals, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among ten animals 1.0weight % suspended in the physiological saline obtained by experiment No.2 Zero animal, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among ten animals 3.0weight % suspended in the physiological saline obtained by experiment No.3 Zero animal, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among ten animals 1.0weight % suspended in PBS obtained by experiment No.4 One animal, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among ten animals 3.0weight % suspended in PBS obtained by experiment No.5 Zero animal, Hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers among ten animals 1.0weight % suspended in the physiological saline obtained by experiment No.9 One animal, Hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers among ten animals 3.0weight % suspended in the physiological saline obtained by experiment No.10 One animal, 3.0 weight % to which the with 1.0 weight % and a mean particle diameter of 100 micrometers hyaluronic acid gel slurry suspended in PBS obtained by experiment No.11 was suspended in PBS obtained by one animal and experiment No.12 among ten animals, It was suggested that there is an adhesion prevention operation hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers excelled [operation] in one animal and hyaluronic acid gel slurry among ten animals.

[0050]1.0 weight % suspended in the physiological saline obtained by adhesion preventive effect test experiment No.2 by the rat cecum model of the adhesion inhibitor of work-example 6 hyaluronic-acid gel slurry, 3.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers and the physiological saline obtained by experiment No.3, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers, 1.0 weight % suspended in PBS obtained by experiment No.4, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers, 3.0 weight % suspended in PBS obtained by experiment No.5, 1.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers and the physiological saline obtained by experiment No.9, 3.0 weight % suspended in hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and the physiological saline obtained by experiment No.10, Hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers, 1.0 weight % suspended in PBS obtained by experiment No.11, The examination was presented with the hyaluronic acid aqueous solution 1.0weight % as hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and comparison 3.0weight % suspended in PBS obtained by hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers and experiment No.12.

[0051]A 10 weeks-old male Wistar rat (weight of about 250g) is made an incision in the abdomen by postanesthetic midline incision in the abdominal cavity by ketamine (60 mg / weight of 1 kg), and KISHIRAJIN (10-mg / weight of 1 kg) injection, Gall until it grinds an about 10x10-mm field against a cecum with a gauge (about 20 times) and punctiform bleeding arises was built. A hyaluronic acid aqueous solution and 2 ml of hyaluronic acid gel slurry were added to the damaged area, and the closed belly was carried out to the rat of each five groups in 3-0 DEKISON.

[0052]The resumption belly of the abdomen was carried out for the rat which prescribed slurry of no taking a measure and a hyaluronic acid gel, and a hyaluronic acid aqueous solution for the patient after five-animal each slaughter on the 14th day of after the operation, and the existence of adhesion formation was judged. The very slight adhesion with filmy adhesion formation was not judged to be adhesion, but it was fibrous, and was thick and the case where the strong adhesion which is not easily stripped as **** with pincettes was produced was judged to be adhesion. The result is shown in Table 4.

[0053]

[Table 4]

実験No.	実験群	癒着発生匹数	備考
33	無処置群	5／5	比較例
34	ヒアルロン酸水溶液	3／5	比較例
35	実験No. 2	1／5	実施例
36	実験No. 3	0／5	実施例
37	実験No. 4	0／5	実施例
38	実験No. 5	1／5	実施例
39	実験No. 9	0／5	実施例
40	実験No. 10	0／5	実施例
41	実験No. 11	0／5	実施例
42	実験No. 12	1／5	実施例

[0054]From Table 4, when the formation rate of adhesion with no taking a measure is five animals among five animals, a hyaluronic acid aqueous solution among five animals 1.0weight % Three animals, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among five animals 1.0weight % suspended in the physiological saline obtained by experiment No.2 One animal, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among five animals 3.0weight % suspended in the physiological saline obtained by experiment No.3 Zero animal, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among five animals 1.0weight % suspended in PBS obtained by experiment No.4 Zero animal, Hyaluronic acid gel slurry with a mean particle diameter of 300 micrometers among five animals 3.0weight % suspended in PBS obtained by experiment No.5 One animal, Hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers among five animals 1.0weight % suspended in the physiological saline obtained by experiment No.9 Zero animal, Hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers among five animals 3.0weight % suspended in the physiological saline obtained by experiment No.10 Zero animal, With 3.0 weight % to which hyaluronic acid gel slurry with a mean particle diameter of 100 micrometers was suspended in PBS obtained by zero animal and experiment No.12 among five animals, and a mean particle diameter of 100 micrometers hyaluronic acid gel slurry among five animals 1.0weight % suspended in PBS obtained by experiment No.11 One animal, It was suggested that there is an adhesion prevention operation which was excellent in hyaluronic acid gel slurry.

[0055]
[Effect of the Invention]As mentioned above, let the poorly soluble hyaluronic acid gel formed by a hyaluronic acid independent be slurry in this invention.
Therefore, the high biomedical material of especially biocompatibility is obtained.

[Translation done.]